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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/763,210	10/16/2001	Shian-Jiun Shih	A2922AUS	2753

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EXAMINER	
NGUYEN, DAVE TRONG	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 03/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/763,210	SHIH ET AL.	
	Examiner	Art Unit	
	Dave T. Nguyen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *32 and 33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claims 1-25 have been amended by the amendment filed December 13, 2004.

Claims 32-33, drawn to non-elected claimed invention, are withdrawn from further consideration by the Examiner, 37 C.F.R. 1.142(b), as being drawn to a non-elected invention. A complete response to the final rejection must include cancellation of non-elected claims or other appropriate action (37 CFR 1.144) MPEP 821.01.

Elected claims 1-31 are pending for examination.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the

> subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6, 22, 25-28 remain rejected under 35 USC 102(a) as being anticipated by WO 97/33975 (Crespo, for which US 6,248,588 B1 is its English version).

The claims are directed to a composition for use in preserving and cryoprerservation of adenoviral vectors/particles that are for use in an *in vivo* injection, wherein the composition comprises mainly a saline solution or buffer and human serum albumin. Crespo teaches the same throughout the disclosure, *e.g.,* abstract, column 2, lines 21-24 of the patent, page 10 of the WO document. Column 6, lines 16-36 of the patent discloses that the composition comprises from 10 to 90% by volume of the saline or buffered solution respectively of human serum albumin solution at 20% (also see page 10 of the WO document. Thus, as a whole the composition disclosed in Crespo

embraces the concentration limitations as listed in claims 2-5. Adenoviral vectors or particles are disclosed on columns 6 and 7 of the patent and page 12 of the WO document. On column 6 or page 10 bridging page 11, the buffered solution contains between 0.5 and 5% by weight of sucrose. The buffered solution also can be made to contain sodium chloride (NaCl), potassium chloride, and/or magnesium chloride ($MgCl_2$), pages 3 and 4 of the WO document. Column 8, lines 55-60, or page 14 of the WO document discloses that the adenoviral vectors can be admixed with any of the disclosed buffered solution for their preservation. Crespo as a whole teaches that the composition can be used for storage, thawing and subsequently for a direct injection of the adenoviral vectors in a subject, whereby the adenoviral vectors are free of contaminants and toxic agents, and thus, are stabilized in performing their intended biological function, *e.g.,* delivery and expression of a gene product of choice.

Applicant's response (pages 10 and 11) has been considered by the examiner, but is not found persuasive. Mainly, applicant asserts that Crespo does not teach "adenoviral vector" but rather just viral particles, and that by describing "biological materials" and/or "viable" materials, Crespo does not teach DNA, vectors, or nucleic acids. However, applicant appears to conveniently and/or narrowly to interprete the teaching of Crespo. A close review of the Crespo reference does teach as a whole that viral particles and/or nucleic acid vectors (which are used interchangeably in the prior art) as carriers of nucleic acids for use in gene transfer and/or gene therapy. It is well-established in the prior art that replicat! ion defective and/or recombinant adenovirus vectors are the same as adenoviral particles. See numerous prior art of record. The

fact that Crespo does not mention DNA, RNA, nucleic acid, oligos, antisense molecules does not necessarily mean that the Crespo reference does not anticipate the claimed invention. The main issue is whether or not a method for preparing a stabilized recombinant adenovirus vector, hence adenoviral particles, by using a recombinant HSA is patentable. This main concept is clearly taught in Crespo, regardless whether or not Crespo is also focused in using HSA to stabilize viable cells and/or viable biological materials. Thus, the rejection remains proper.

Claims 1, 6-17, 22-24, 25, 26, 29-31 remain rejected under 35 USC 103(a) as being unpatentable over Crespo in view Engler (US 2003/0211598 A1).

Crespo is applied to the base claims as set forth above. Crespo does not teach that Tris-HCl buffer can be used as a saline solution, that the pH of the solution is 7.5 or greater than 7.5 such as 8.0, 8.2, and 8.4. Crespo also does not teach that the gene product of choice is p53 or HSV-TK.

However, at the time the invention was made, Engler teaches that a pharmaceutical buffer such as Tris-HCl, which contains 1-3 mM MgCl2, at a about ph 6.4-8.4 is suitable for use as a buffer to contain adenoviral vectors, pars. 0031, 0032, page 3. Engler also teaches that the adenoviral vector can be used to deliver and express HSV-Tk or p53.

It would have been obvious for one of ordinary skill in the art to employ a suitable pharmaceutical buffer such as Tris-HCl and/or 2mM MgCl2 at about pH 7.5, 8.0, 8.2 or

8.4 as the saline solution employed in Crespo. One of ordinary skill in the art would have been motivated to employ Tris-HCl and/or 2mM MgCl2 at about pH 7.5, 8.0, 8.2 or 8.4 because Crespo teaches as long as a saline solution is compatible to an *in vivo* environment, and contains the necessary ingredients as required such as salts, and/or MgCl2, the saline solution is suitable for use as a storing and/or preserving buffer of adenoviral vectors. As such, and since Engler teaches that Tris-HCl is a pharmaceutically acceptable solution, *e.g.,* compatible ! for use pharmaceutically or *in vivo,* and that a pH of the buffer such as those in the range of 6.4 to 8.4 is pharmaceutically acceptable for use in containing and delivering the adenoviral vectors, one of ordinary skill in the art would have been motivated to employ a Tris-HCl buffer containing a suitable amount of $MgCl_2$ such as 2mM at a suitable pH such as pH of 8.4 as the saline solution in Crespo. One of ordinary skill in the art would have a reasonable expectation of success in employing the Tris-HCl/NaCl/MgCl2/HAS based solution in preserving and storing adenoviral vectors because each of the ingredients employed in the solution is expected to help stabilize and/or enhance the intended function of adenoviral vectors, as taught as a whole by the combined cited references

Thus, the claimed invention as a whole was *prima facie* obvious.

Applicant's assertion (page 13) has been considered by the examiner but also is not found persuasive. Applicant mainly asserts that the rejection is base on a combination use of both the buffers of Crespo and Engler. However, such is not correct because the main issue is whether or not a person of ordinary skill in the art would have been motivate to employ Tris-HCl and/or 2mM MgCl2 at about pH 7.5, 8.0,

8.2 or 8.4 as a buffer for use in preparing adenoviral vectors containing a transgene for *in vivo* gene transfer protocols. Since Engler teaches that Tris-HCl is a pharmaceutically acceptable solution, *e.g.,* compatible for use pharmaceutically or *in vivo,* and that a pH of the buffer such as those in the range of 6.4 to 8.4 is pharmaceutically acceptable for use in containing and delivering the adenoviral vectors, one of ordinary skill in the art would have been motivated to employ a Tris-HCl buffer containing a suitable amount of $MgCl_2$ such as 2mM at a suitable pH such as pH of 8.4 as the saline solution in Crespo. One of ordinary skill in the art would have a reasonable expectation of success in employing the Tris-HCl/NaCl/MgCl2/HAS based solution in preserving and storing adenoviral vectors because each of the ingredients employed in the solution is expected to help stabilize and/or enhance the intended function of adenoviral vectors, as taught as a whole by the combined cited references! . The examiner is not aware of any evidence showing that the Tris-HCl and/or 2mM MgCl2 at about pH 7.5, 8.0, 8.2 or 8.4 as a buffer would denature the recombinant HSA for use in preserving adenoviral particles. If such is the case, applicant is invited to provide such evidence. Note that the evidence, if such exists, would also shows that the claimed invention is not enabling under 35 USC 112, first paragraph.

Claims 1-31 are rejected under 35 USC 103(a) as being unpatentable over Crespo taken with Engler and further in view of Rolland (US 6,040,295) or Sene (WO 98/02522, wherein its English version is US 6,451,256)

Crespo in combination with Engler is applied to the base claims as set forth above. Crespo in combination with Engler does not teach that a basis pH between 8 and 9 of a suitable buffer would stabilize adenoviral vectors, and that 150 mM of NaCl would function as a stabilizer of adenoviral vectors.

However, at the time the invention was made, Rolland teaches that a typical isotonic saline solution has 150 mM NaCl (column 5, first par.). In addition, Sene teaches that Tris-HCl Buffer is one of many suitable buffer or aqueous solution that can be used to enhance the stability of adenoviral vectors, and that the recombinant adenovirus vectors gain in stability when the aqueous solution used has a basis pH of between 9 and 9, preferably 8.5, and that 2 mM $MgCl_2$ and/or 150 mM of NaCl once employed in the solution are the stabilizers (column 3, second par., fourth par., and lines 33-50).

It would have been obvious for one of ordinary skill in the art to employ a suitable pharmaceutical buffer such as Tris-HCl, 5% sucrose, 2mM $MgCl_2$ and 150 mM of NaCl at about pH of 8.0, 8.2 or 8.4 as the saline solution employed in Crespo. One of ordinary skill in the art would have been motivated to employ Tris-HCl and/or 2mM $MgCl_2$at about pH 7.5, 8.0, 8.2 or 8.4 because Crespo teaches as long as a saline solution is compatible to an *in vivo* environment, and contains the necessary ingredients as required such as salts, and/or $MgCl_2$, the saline solution, which is typically c! ontains 150 mM NaCl, see Rolland, is suitable for use as a storing and/or preserving buffer of adenoviral vectors. Alternatively, since Engler teaches that Tris-HCl is a pharmaceutically acceptable solution, *e.g.,* compatible for use pharmaceutically or *in*

vivo, and that a pH of the buffer such as those in the range of 6.4 to 8.4 is pharmaceutically acceptable for use in containing and delivering the adenoviral vectors, and since Sene teaches that 2 mM MgCl2 and/or 150 mM NaCl together with the disclosed basic pH would act as stabilizers of adenoviral vectors, one of ordinary skill in the art would have been motivated to employ a Tris-HCl buffer containing a suitable amount of $MgCl_2$ such as 2mM, of 150 mM NaCl at a suitable basic pH ! such as pH of 8.4 as the saline solution in Crespo. One of ordinary skill in the art would have a reasonable expectation of success in employing the Tris-HCl/NaCl/ $MgCl_2$/HAS based solution in preserving and storing adenoviral vectors because each of the ingredients employed in the solution is expected to help stabilize and/or enhance the intended function of adenoviral vectors, as taught as a whole by the combined cited references

Thus, the claimed invention as a whole was *prima facie* obvious.

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE **THREE MONTHS** FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUORY PERIOD FOR RESPONSE EXPIRE LATER THAN **SIX MONTHS** FROM THE DATE OF THIS FINAL ACTION.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **571-272-0731**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Amy Nelson*, may be reached at **571-272-0184.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center number, which is **703-872-9306.**

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen
Primary Examiner
Art Unit: 1632

DAVE TRONG NGUYEN
PRIMARY EXAMINER